Abstract

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Project Title: Development of a HTS assay for Inhibitors of bacterial DnaK

Abstract: *DESCRIPTION* (provided by applicant): Antibiotic resistance is a major concern that has influenced both the clinical uses of established antimicrobials and the development of new agents. In clinical settings, gram-negative bacteria were a major problem in the 1970's, whereas the past decades have seen a climb in the number of incidents with multidrug resistant gram-positive strains. Currently, the rapid emergence of resistant strains involves both grampositive and gram-negative pathogens. It is not an overstatement to claim that one of the most serious, and urgent, topics in clinical and vetinary health is the timely development of antibacterial compounds that kill bacteria in a manner completely different from those utilized by the currently marketed antimicrobial compounds. The goal of this program application is to advance the knowledge and utilization of DnaK inhibitors as the next generation of antibacterial agents. Our previous efforts in this field have demonstrated the validity of DnaK inhibitors as antimicrobial agents, albeit in the realm of peptide-based inhibitors. By advancing this effort, and the anticipated small molecule DnaK inhibitors, into the academic realm it is expected that a more thorough and precise understanding of the role of microbial chaperone systems in the procession of pathogenic infections will result, thereby allowing a greater understanding of the role of environmental adaptations in the establishment of such disease states. Through optimization and validation of the preliminary screening format a viable HTS protocol will be developed that may be applied to a number of diverse homologs of E.coli DnaK, leading to a family of HTS formats for the identification and optimization of organism-selective antimicrobial agents. It is the goal of Chaperone Technologies to develop these agents as effective antimicrobial treatments for clinically significant drug-resistant infections such as E.coli and K.pneumoniae drug-resistant urinary-tract infections, MRSA infections and VRE/GRE infections. The occurrence of such clinical infections is rapidly increasing and will represent a major challenge in the coming years. It is forecast that the current generation of antibiotics will not be sufficiently active to adequately control these cases, necessitating the discovery and development of fundamentally novel antimicrobial agents.

Thesaurus Terms:
High throughput screening, Antibiotic resistance, antimicrobials, gram-positive strains, DnaK inhibitors, E.coli, DnaK, K.pneumoniae, urinary-tract infections, MRSA infections, VRE/GRE infections

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